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(54) Title: SYNTHETIC METHOD FOR DIRECT ARYLATION OF HETEROCYCLIC ARENES

(57) Abstract: Methods for the direct, selective arylation of carbon-hydrogen sites on various heteroaromatic compounds are disclosed. A method of the present invention includes contacting the heteroaromatic compound with a basic compound to form a first mixture, adding a second mixture comprising a catalyst to the first mixture to form a third mixture, and adding an Ar-X compound to the third mixture, wherein Ar comprises an aryl species and X comprises a leaving group.

SYNTHETIC METHOD FOR DIRECT ARYLATION OF HETEROCYCLIC ARENES

RELATED PATENT APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/444,542, filed February 3, 2003 and entitled "Synthetic Method for Direct Arylation of Heterocyclic Arenes".

ACKNOWLEDGEMENT

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TECHNICAL FIELD

The present disclosure relates generally to the synthesis of complex organic molecules and more particularly to novel methods of direct arylation of selected carbon-hydrogen sites on heteroaromatic compounds.

BACKGROUND

One group of complex organic molecules that have particular importance in numerous industries are heteroarenes. Heteroarenes are heterocyclic compounds that may be derived from arenes by replacement of one or more methine (-C=) and/or vinylene (-CH=CH-) groups by trivalent or divalent heteroatoms, respectively, so as to maintain the continuous electron system characteristic of aromatic systems. Heteroarenes represent structural units frequently found in a broad range of organic compounds, including natural products, pharmaceuticals, dyes, and other functional synthetics.

Heteroarenes present unique challenges in organic synthesis because of different reactivity of the heteroatoms (*e.g.* nitrogen, oxygen, sulfur, phosphorous) compared with the carbon atoms on the ring. Arylation of the heteroarene will typically occur at the most reactive site of the heteroarene, which for azoles is the

typically occur at the most reactive site of the heteroarene, which for azoles is the nitrogen site. This situation leads to unique problems when one desires to add the aryl group to a second position on the heteroarene.

Known processes to arylate the carbon on the heteroarene typically involve placing a reactive group on the carbon site that desires to be arylated (Suzuki and Stille reactions). Another known process requires adding a protective group to the heteroatom in a separate process before arylation can proceed.

Known processes have numerous disadvantages. First, most processes suffer from low selectivity and low yields. Second, known process cannot be done directly but require pre-treatment steps which results in a more inefficient reaction. Lastly, traditional catalysts and bases used in arylation reactions are comparatively expensive.

SUMMARY

The present invention is directed to, according to one embodiment, a method for the direct arylation of carbon-hydrogen sites on a heteroaromatic compound. The method includes contacting the heteroaromatic compound with a basic compound to form a first mixture, adding a second mixture comprising a catalyst to the first mixture to form a third mixture, and adding an Ar-X compound to the third mixture, wherein Ar comprises an aryl species and X comprises a leaving group. The second mixture may further comprises a carbon selectivity agent, which is preferably copper iodide. The basic compound may include oxides, carbonates, carboxylates (such as acetates and pivaloates) and salts. The catalyst may include transition metal catalysts. In certain embodiments, the leaving group is a halogen or triflate.

According to another embodiment, a palladium-catalyzed method for selectively arylating a N-H heteroaromatic compound having at least a first carbon-hydrogen site and a second carbon-hydrogen site for arylation is disclosed. The method includes forming a mixture comprising the heteroaromatic compound and a basic compound, adding a palladium catalyst to the mixture, adding a carbon

selectivity agent to the mixture if arylation is desired on the second carbon-hydrogen site, and adding an Ar-X compound to the mixture. In certain embodiments, the catalyst may be palladium acetate and the basic compound is magnesium oxide or zinc oxide.

According to one embodiment, a method for a cobalt-catalyzed method for the selective arylation of an imidazole or a dervivative of imidazole is disclosed. In certain embodiments, the cobalt catalyst is cobalt acetate and the basic compound is magnesium oxide or zinc oxide.

According to another embodiment, a cobalt-catalyzed method for the selective arylation of a heteroaromatic compound that does not have a free N-H site. In exemplary embodiments, the heteroaromatic compound that does not have a free N-H site is selected from the group consisting of oxazoles, thiazoles, benzoxazoles and benzthiazoles. In other embodiments, the cobalt catalyst is cobalt acetate and the basic compound is cesium carbonate.

According to an embodiment of the present invention, a method for the selective arylation of an oxazole or a 2-functionalized oxazole is disclosed. In certain embodiments, the catalyst is palladium acetate and the basic compound comprises cesium carbonate. The method may further include a 2-(dicyclohexylphosphino)biphenyl ligand and an arylchloride.

According to another embodiment of the present invention, a method for the selective arylation of a N-functionalized indole is disclosed. In certain embodiments, the catalyst is palladium acetate and the basic compound is cesium acetate.

According to a method of the present invention, a method of making a pharmaceutical product is disclosed. The method includes contacting a heteroaromatic compound with a basic compound to form a first mixture, adding a second mixture comprising a catalyst to the first mixture to form a third mixture and adding an Ar-X compound to the third mixture, wherein Ar comprises an aryl species and X comprises a leaving group.

According to another embodiment, a method of making a dye is disclosed. In certain embodiments the dye may be a brighter, a fluorescent dye, a dye

used for liquid crystal materials or a dye used for paint products.

According to an embodiment, the present invention discloses a method of making a nanotechnology material. In one embodiment, the nanotechnology material is a material used in a single molecule information storage device.

DETAILED DESCRIPTION

The present invention provides for methods of direct arylation of carbon-hydrogen sites on heteroaromatic compounds to give arylated heteroarenes. The present invention also allows for high selectivity of the carbon-hydrogen site desired to be arylated. Certain methods of the present invention may avoid many problems associated with previous methods for arylating heteroaromatic compounds. The present methods eliminate the requirement of having a reactive group at the carbon site of aryl group attachment. The methods developed for free azoles (Examples 1-4) also eliminate the requirement to portect nitrogen in the heteroarene in a pre-treatment reaction. Embodiments of the present invention allow for increased yields and high selectivity of arylation of a desired carbon site. Certain methods also allow for use of cost-efficient catalysts and reagents.

Numerous industries may use methods of the present invention for the efficient preparation of arylated heteroarenes. First, arylated heteroarenes are a basic building block for many pharmaceutical products. Additionally, arylated heteroarenes are commonly used in dyes. Dyes may be used in paint products and liquid crystal material. Arylated heteroarenes may have particular importance in brightners such as fluorescent dyes. Furthermore, arylated heteroarenes of the present invention can be used in nanotechnology applications. An example of a nanotechnology application includes using arylated heteroarenes as substrates in single molecule information storage devices.

Methods of the present invention include a heteroaromatic compound, a basic compound, a catalyst and an Ar-X compound. The methods of the present invention may optionally include transition metal ligands and a carbon selectivity agent.

The heteroaromatic compounds of the present invention may include,

for example, a compound containing an aromatic ring having one or more groups Y in the aromatic ring, where each group Y is independently oxygen, sulfur, nitrogen-R, or phophorous-R, where R is a hydrogen, C_{1-20} straight-chain alkyl or branched alkyl; C_{1-20} cycloalkyl, bicycloalkyl, or tricycloalkyl; or aryl, with the proviso that one or more than one oxygen, nitrogen, sulfur and nitrogen-R group, independently or in various combinations, may be present in the aromatic ring. Examples of suitable heteroaromatic compounds include indoles, imidazoles, pyrroles, oxazoles, pyrazoles, triazoles, tetrazoles, thioazoles, benzthiazoles, more complex fused bicyclic analogs of above mentioned compounds, other polycyclic-fused arenes and combinations thereof. Imidazoles include, but are not limited to, 2-arylimidazole, 4-phenylimidazole, benzimidazole, other analogs and derivatives thereof. Other examples of suitable heteroaromatic compounds are shown in the Tables in the Examples Section below. For the purposes of this disclosure, a N-H heteroaromatic refers to a heteraromatic compound with at least one nitrogen-hydrogen site on the ring. Derivatives of certain heteroaromatic compounds refer to any compound that includes the heteroaromatic compound as a component or any compound that was obtained from a reaction of the heteroaromatic compound. For the purposes of this invention, heteroaromatic compounds also include any of the compounds listed above with one or more additional functional groups attached. One skilled in the art, with the benefit of this disclosure, will recognize other suitable heteroaromatic compounds for a particular application.

The basic compound in the present invention may be any suitable compound capable of suppressing the reactivity of the most reactive site on the heteroaromatic compound. The basic compound may be, for example, an oxide, a carbonate, a carboxylate or a salt. Examples of suitable oxides include magnesium oxide (MgO) and zinc oxide (ZnO). An example of a suitable carbonate includes cesium carbonate(Cs_2CO_3). Carboxylates include, but are not limited to acetates and pivaloates. Examples of suitable acetates include cesium acetate (CsOAc) and potassium acetate (KOAc). Examples of suitable salts may include magnesium salts or zinc salts. Basic compounds may also comprise any magnesium or zinc based compound.

The choice of which basic compound to use in a particular application depends, *inter alia*, on the heteroaromatic compound desired to be arylated and the catalyst being used. The basic compound used in an arylation may have a strong influence over the eventual yield and regioselectivity of the product. Therefore, certain methods prefer certain basic compounds to be used.

The following methods illustrate the particular basic compounds preferred for each method of the present invention. In a method to selectively arylate a N-H heteroaromatic compound using a palladium catalyst, a magnesium oxide would be a preferred basic compound. In a cobalt-catalyzed method for the selective arylation of imidazole or a derivative of imidazole, using an oxide such as magnesium oxide or zinc oxide would be preferred with a cobalt acetate catalyst. For a cobalt-catalyzed method of selective arylation of a heteroaromatic compound that does not have a free-N-H site (oxazole, thiazole, benzoxzole and benzthiazole) and where the catalyst is cobalt acetate, a carbonate such as cesium carbonate would be the preferred basic compound. In a method for the selective arylation of a 2-aryl oxazole, where the catalyst is palladium acetate, the basic compound preferably is cesium carbonate. Lastly, in a method for the selective arylation of N-functionalized indoles, where palladium acetate is the catalyst, a carboxylate such as cesium acetate is the preferred basic compound.

Other factors, such as cost and availability of the basic compound, may also determine which basic compound is used for a particular application. For cost-effectiveness, magnesium oxide may be preferred to other basic compounds. One skilled in the art, with the benefit of this disclosure in view of the considerations will be able to choose a particular suitable basic compound for a particular application.

The catalyst of the present invention may comprise any material that serves to facilitate the addition of the aryl species to the heteroaromatic compound. Examples of suitable catalysts include transition metal catalysts. The transition metal catalysts may include, for example, a catalyst containing palladium, cobalt and mixtures thereof. Examples of the transition metal catalyst include palladium acetate ($Pd(OAc)_2$), cobalt acetate ($Co(OAc)_2$) and mixtures thereof. Other transition metal catalysts may include ruthenium, rhodium and iridium. The choice of catalysts used

may depend on the factors such as what heteroaromatic compound is being arylated. Other factors, such as cost and availability, may determine the catalyst used. For example, the cobalt catalyst may be advantageous because of its low-cost, therefore making the reaction more cost-effective. Additional embodiments of the present invention (see Example 8 in Examples Section) have the additional advantage of requiring low catalyst loadings. Example 8 only requires one-tenth the catalyst loading of the reactions in Examples 1-7. It is know to those skilled in the art, having knowledge of the teachings of the present application, how to choose a suitable catalyst for a given reaction.

Embodiments of the present invention include an Ar-X compound. The Ar-X compound utilized in methods of the present invention may comprise any aryl species (Ar) and the a leaving group (X). As used herein, "aryl" or "aryl species" refers to any group obtained from a compound containing a first aromatic ring by removal of a hydrogen from a carbon of the first aromatic ring. The aryl group may contain one or more additional aromatic rings. The one or more additional aromatic rings may be connected to the first aromatic ring by one or more covalent bonds or may be fused to the first aromatic ring, wherein each of the one or more additional aromatic rings fused to the first aromatic ring has two carbon atoms in common with the first aromatic ring. The aryl group may be optionally substituted with a substituent at one or more positions of the first aromatic ring or of the additional aromatic ring or rings, wherein the substituent at each of the one or more positions is independently halogen, R^1, NR^2R^3, OR^4, or SR^5, where each of R^1, R^2, R^3, R^4 and R^5 is independently C_{1-20} straight-chain alkyl or branched alkyl or aryl. The aryl group may be optionally fused to a C_3-C_{20} aliphatic ring, wherein the C_3-C_{20} aliphatic ring has two carbon atoms in common with the first aromatic ring and the number of carbon atoms in the C_3-C_{20} aliphatic ring includes the two carbon atoms in common with the first aromatic ring. Aryl groups includes those compounds represented in Tables 1 and 10 in the Examples Section below, which generally include aromatic iodides with a substituent R on the 2 or 4 position, where the R may be, but is not limited to H, Me, OMe, NMe_2, CF_3, F, and $COCH_3$. Aryl groups may also include previously mentioned heteroaromatic compounds including compounds such as pyridine. Aryl groups include, for example, phenyl, 1-naphthyl, and 2-naphthyl. One

of ordinary skill in the art, with the benefit of this disclosure, will recognize other suitable aryl species for a particular application.

The Ar-X compound also includes a leaving group X. X is a leaving group such as, for example, a halogen or a triflate species. Examples of suitable halogens are iodine, bromine, chlorine and fluorine. One of ordinary skill in the art with the benefit of this disclosure will recognize other suitable leaving groups that may be used in conjunction with a particular application.

Methods of the present invention may optionally include at least one of a variety of transition metal ligands or ligands. The transition metal ligands serve to generate the active catalysts in situ. Examples of suitable transition metal ligands include phosphines (such as triphenyphosphine, dicyclohexylphenyl phosphine and 2-(dicyclohexylphosphino)biphenyl), SALEN (ethylenebis(salicylimine)), nitrogen ligands (such as bipyridine), carbene ligands (such as IMes) and other ligands shown in the Tables in the Examples Section below. A ligand may be chosen depending on the catalyst used in a particular application. For example, a phosphine ligand, such as triphenyphosphine, may be preferred with a palladium acetate catalyst and a magnesium oxide or a cesium acetate basic compound. For an application that includes a palladium acetate catalyst and a cesium carbonate basic compound, another phosphine ligand such as 2-(dicyclohexylphosphino)biphenyl) may be preferred. Cobalt catalysts may prefer ligands such as SALEN or IMes. In the reaction of 2-aryl oxazole, using the ligand 2-(dicyclohexylphosphino)biphenyl) allows Ph-Cl to be used as the Ar-X compound. This is important because previous methods did not allow for use of arylchlorides. One skilled in the art, with the benefit of this disclosure will recognize other suitable transition metal ligands for a particular application.

Methods of the present invention may optionally include a carbon selectivity agent. A carbon selectivity agent allows for regioselectivity of the particular carbon site for arylation. An example of a suitable carbon selectivity agent comprises copper iodide. Those of ordinary skill in the art having knowledge of the teachings of the present invention will know other suitable carbon selectivity agents that may be used in conjunction with a particular application.

Embodiments of methods developed for free azoles in the present invention (Examples 1-4) include treating a heteroaromatic compound with a basic compound to form a first mixture. By contacting the heteroaromatic compound with the basic compound, the basic compound may nuetralize the reactivity of the heteroatom or heteroatoms of the heteroaromatic compound. By suppressing the reactivity of the heteroatom, arylation is less likely to occur at the heteroatom site. The basic compounds interacting with the heteroatom may also increase the reactivity of an adjacent carbon-hydrogen bond.

Some methods of the present invention include adding to the first mixture a second mixture to form a third mixture. The second mixture includes a catalyst. The catalyst may coordinate with a carbon-hydrogen site to assist with the arylation of the carbon-hydrogen site.

In an alternative embodiment of the present invention, the second mixture includes a catalyst and a carbon selectivity agent. The carbon selectivity agent may allow for highly selective arylation of a second aylation site on the heteroaromatic compound. A heteroaromatic compound may have at least two arylation sites that are suitable for arylation. Typically one site will be more apt to arylate. A carbon selectivity agent may accomplish arylation of a second carbon-hydrogen site by selectively targeting that site of the heteroaromatic compound, therefore causing arylation to occur on the second most reactive carbon-hydrogen site. By changing the second mixture so as to contain a carbon selectivity agent, the methods of the present invention may allow for regioselectivity of the arylation. As an example of the above methods, the arylation at the 2-position of imidazole and benzimidazole can be obtained with a mixture containing the basic compound, the catalyst and copper iodide.

The methods of the present invention include adding an Ar-X compound to the third mixture. The Ar-X compound has a leaving group X. Once the catalyst inserts itself between the Ar-X bond, the resulting aryl-catalyst species will arylate at the desired reaction site on the heteroaromatic compound, thereby forming the desired heteroarene.

The methods of the present invention may also include additional

steps, *inter alia*, heating the mixture and purifying the mixture.

An example method of the present invention includes a palladium-catalyzed method for selectively arylating a N-H heteroaromatic compound having at least a first carbon-hydrogen site and a second carbon-hydrogen site for arylation. The method includes forming a mixture of the heteroaromatic compound and a basic compound, adding a palladium catalyst to the mixture, adding a carbon selectivity agent to the mixture if arylation is desired on the second carbon-hydrogen site, and adding an Ar-X compound to the mixture. In certain exemplary embodiments of the method, the N-H heteroatomic compound is an indole, imidazole, 2-arylimidazole, 4-phenylimidazol, benzimidazole, pyrrole, or pyrazole. In other exemplary embodiments of the present invention, the palladium catalyst is palladium acetate, the carbon selectivity agent is copper iodide, and the basic compound is magnesium oxide or zinc oxide. The method may further comprise adding a phosphine ligand to the mixture.

In another example method of the present invention includes a cobalt-catalyzed method for the selective arylation of an imidazole having at least a first carbon-hydrogen site and a second carbon-hydrogen site for arylation. The method includes forming a mixture comprising the imidazole compound and a basic compound, adding a cobalt catalyst to the mixture, adding a carbon selectivity agent to the mixture if arylation is desired on the second carbon-hydrogen site, and adding an Ar-X compound to the mixture. The imidazole may be a derivative of imidazole. In certain embodiments of the present invention the cobalt catalyst is cobalt acetate and the basic compound is magnesium oxide or zinc oxide. The method may further comprise adding a SALEN or IMes ligand to the mixture.

In an example method of the present invention, a cobalt catalyzed method is disclosed for the selective arylation of a heteroaromatic compound that does not have a free N-H site, the heteroaromatic compound having at least a first carbon-hydrogen site and a second carbon-hydrogen site for arylation. The method includes forming a mixture comprising the heteroaromatic compound and a basic compound, adding a cobalt catalyst to the mixture, adding a carbon selectivity agent to the mixture if arylation is desired on the second carbon-hydrogen site, and adding

an Ar-X compound to the mixture. The heteroaromatic compound that does not have a free N-H site includes oxazoles, thiazoles, benzoxazoles and benzthiazoles. In certain embodiments of the present invention the cobalt catalyst is cobalt acetate and the basic compound comprises cesium carbonate. The method may further include adding a SALEN or IMes ligand to the mixture.

In another example method of the present invention, a method is disclosed for the selective arylation of a 2-aryl oxazole having at least a first carbon-hydrogen site and a second carbon-hydrogen site for arylation. The method includes forming a mixture comprising the 2-aryl oxazole and a basic compound, adding a catalyst to the mixture, adding a carbon selectivity agent to the mixture if arylation is desired on the second carbon-hydrogen site, and adding an Ar-X compound to the mixture. In certain exemplary embodiments of the present invention, the catalyst is palladium acetate. In some embodiments, the basic compound is cesium carbonate. The method may further comprise adding a 2-(dicyclohexylphosphino)biphenylligand to the mixture. In another embodiment, the Ar-X compound is chlorobenzene.

A method of the present invention includes the selective arylation of a N-functionalized indole having at least a first carbon-hydrogen site and a second carbon-hydrogen site for arylation. The method includes forming a mixture comprising the N-functionalized indole and a basic compound, adding a catalyst to the mixture, adding a carbon selectivity agent to the mixture if arylation is desired on the second carbon-hydrogen site, and adding an Ar-X compound to the mixture. In an embodiment the catalyst is palladium acetate. In another embodiment, the basic compound is cesium acetate.

An example method of the present invention includes a method of making a pharmaceutical product comprising contacting a heteroaromatic compound with a basic compound to form a first mixture, adding a second mixture comprising a catalyst to the first mixture to form a third mixture, and adding an Ar-X compound to the third mixture, wherein Ar comprises an aryl species and X comprises a leaving group.

Another example method of the present invention includes a method of making a dye comprising contacting a heteroaromatic compound with a basic

compound to form a first mixture, adding a second mixture comprising a catalyst to the first mixture to form a third mixture, and adding an Ar-X compound to the third mixture, wherein Ar comprises an aryl species and X comprises a leaving group. In one embodiment, the dye is a fluorescent dye. In another embodiment, the dye is a dye used for liquid crystal materials. In yet another embodiment, the dye is a dye used for paint products.

An example method of the present invention includes a method of making a nanotechnology material comprising contacting a heteroaromatic compound with a basic compound to form a first mixture, adding a second mixture comprising a catalyst to the first mixture to form a third mixture, and adding an Ar-X compound to the third mixture, wherein Ar comprises an aryl species and X comprises a leaving group. In one embodiment, the nanotechnology material is a material used in a single molecule information storage device.

This invention is useful as a method for the efficient preparation of arylated heteroarenes in numerous indusries. First, arylated heteroarenes are a basic building block for many pharmaceutical products. Additionally, arylated heteroarenes are commonly used in dyes. Dyes may be used in paint products and liquid crystal material. Arylated heteroarenes may have particular importance in brightners such as fluorescent dyes. Furthermore, arylated heteroarenes of the present invention can be used in nanotechnology applications. An example of a nanotechnology application includes as using arylated heteroarenes in a single molecule information storage device.

The methods of the present invention may be conducted in a variety of organic solvents, which may be, for example, dipolar aprotic organic solvents. Examples of dipolar aprotic organic solvents include dimethyl formamide, dioxane, tetrahydrofuran, dimethylacetamide, and acetonitrile.

The methods of the present invention may be advantageously used, for example, for the arylation of heteroarenes containing one or more N-H functionalities, which may not be readily arylated by known methods without first protecting the one or more N-H functionalities. Examples of heteroarenes containing N-H functionalities which may be arylated by the method of the invention include indole,

imidazole, 2-arylimidazoles, 4-phenylimidazole, benzimidazole, pyrrole. Heteroarenes containing N-H functionalities outside of the ring may also be arylated by the method of the invention. In the method of the invention, an aryl substituent is attached to the heteroarene nucleus in a manner which eliminates the requirement of a reactive functionality at the *ipso* position of the heteroarene nucleus, which is the position at which the aryl substituent becomes attached.

To facilitate a better understanding of the present invention, the following examples of preferred embodiments are given. In no way should the following examples be read to limit or define the scope of the invention.

EXAMPLES

Examples 1-8 and the examples shown in the following Tables 1-11 herein further illustrate example embodiments of the present invention.

Examples 1 and 2 are the suitable methods for selective arylation of NH-heteroarenes such as indole, imidazole, pyrazole, pyrrole. Furthermore, heteroarenes may be selectively arylated by the method of the invention at one position out of two or more possible positions by applying different reaction conditions. For example, in the case of imidazoles, arylation may occur at either position 2 or 4 of the imidazole ring by applying different reaction conditions. For example, the 4-position of imidazole may be arylated under conditions listed in Table 1, Chart C: entry 3 below (experimental procedure called as Example 1), using $Pd(OAc)_2$ as the catalyst, Ph_3P (triphenylphosphine) as the ligand, MgO as the base, and dioxane as the solvent. A switch in regioselectivity, resulting in arylation of the 2-positions of imidazole, benzimidazole, and purines is achieved by using conditions listed in Table 1, Chart C: entry 5 (experimental procedure called as Example 2), whereby CuI (copper iodide) is added to the reagents of Chart C: entry 3.

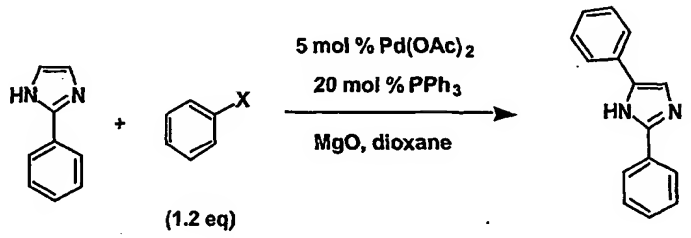
Examples 3 and 4 are the suitable methods for selective cobalt-catalyzed arylation of imidazole and derivatives of imidazole.

Examples 5 and 6 are the suitable methods for selective cobalt-catalyzed arylation of heteroarenes that do not contain free nitrogen-hydrogen sites (such as oxazoles, thiazoles, benzoxazoles and benzthiazoles).

Example 7 is the suitable method for selective arylation of 2-aryl oxazoles.

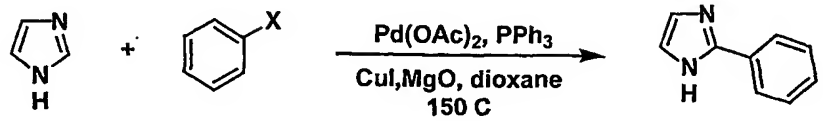
Example 8 is the suitable method for selective arylation of N-functionalized indoles.

Example 1: Catalytic arylation of 2-Phenyl imidazole with $Pd(OAc)_2$



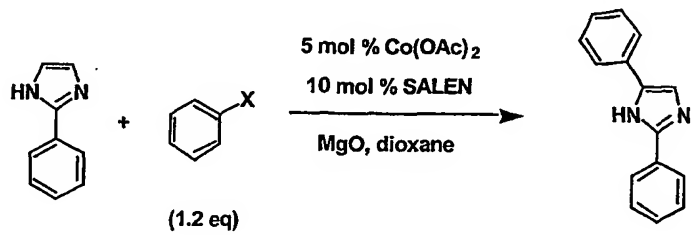
In a flame dried flask, 2-phenyl imidazole (50 milligram (mg), 0.347 milli-mol (mmol)) and MgO (16.8 mg, 0.416 mmol, 1.2 equiv) were suspended in 1 milliliter (ml) dry dioxane and stirred at room temperature for 10 minutes (min) to form a first mixture. $Pd(OAc)_2$ (3.9 mg, 0.017 mmol, 5 mol %) and PPh_3 (18.2 mg, 0.069 mmol, 0.2 equiv) were added to the first mixture in an argon ambient to form a second mixture. Phenyl iodide (84.9 mg, 0.416 mmol, 1.2 equiv) was dissolved in 0.5 ml dry dioxane and added dropwise to the second mixture to form a third mixture. The third mixture was heated to 150°C in an argon ambient. The reaction propagation was monitored by TLC and upon completion (after about 12 hours) of the reaction, the resulting mixture was diluted with $CHCl_3$ (20 ml) and filtered through a pad of celite. The solvents were evaporated and the product (62.6 mg, 82 %) was isolated by flash column chromatography (gradient elution hexanes → 20 % ethyl acetate / 80 % hexanes).

Example 2: Catalytic arylation of imidazole at C-2



In a flame dried flask, imidazole (30 mg, 0.441 mmol) and MgO (21.3 mg, 0.529 mmol, 1.2 equiv) were suspended in 1 ml dry dioxane and stirred at room temperature for 10 minutes to form a first mixture. CuI (167.8 mg, 0.881 mmol, 2 equiv), $Pd(OAc)_2$ (4.9 mg, 0.022 mmol, 5 mol %) and PPh_3 (23.1 mg, 0.088 mmol, 0.2 equiv) were added to the first mixture under argon with vigorous stirring to form a second mixture. Phenyliodide (107.9 mg, 0.529 mmol, 1.2 equiv) was dissolved in 0.5 ml dry dioxane, added dropwise to the second mixture to form a third mixture. The third mixture was heated to 150 °C under argon. The reaction propagation was monitored by TLC and upon completion (after about 12 hours, when the relative amount of desired product reached its maximum, longer reaction times may lead to further arylation of the product), the crude mixture was diluted with $CHCl_3$ (20 ml) and filtered through a pad of celite. The solvents were evaporated and the 2-phenylimidazole (52.7 mg, 83 % yield) was isolated by flash column chromatography (gradient elution hexanes → 20 % ethyl acetate / 80 % hexanes).

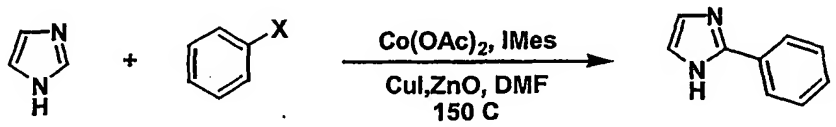
Example 3: Catalytic arylation of 2-Phenyl imidazole with $Co(OAc)_2$



In a flame dried flask, 2-phenyl imidazole (50 mg, 0.347 mmol) and

MgO (16.8 mg, 0.416 mmol, 1.2 equiv) were suspended in 1 ml dry dioxane and stirred at room temperature for 10 min to form a first mixture. Anhydrous $Co(OAc)_2$ (3.1 mg, 0.017 mmol, 5 mol %) and SALEN (9.3 mg, 0.035 mmol, 0.1 equiv) in 0.5 ml dry dioxane were stirred for 10 min at room temperature in another flame dried flask and added to the first mixture under argon to form a second mixture. Phenyl iodide (84.9 mg, 0.416 mmol, 1.2 equiv) was dissolved in 0.5 ml dry dioxane and added dropwise to the second mixture to form a third mixture. The third mixture was then heated to 150°C under argon. The reaction propagation was monitored by TLC and upon completion (after about 12 hours) of the reaction, the resulting reaction mixture was diluted with $CHCl_3$ (20 ml) and filtered through a pad of celite. The solvents were evaporated and the product (58.8 mg, 77 %) was isolated by flash column chromatography (gradient elution hexanes → 20 % ethyl acetate / 80 %).

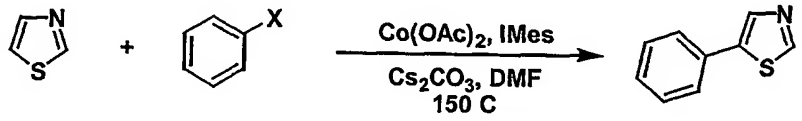
Example 4: Catalytic arylation of imidazole at C-2 with $Co(OAc)_2$ / IMes / CuI



In a flame dried flask, anhydrous $Co(OAc)_2$ (3.9 mg, 0.022 mmol, 5 mol %), 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride Cl (15.0 mg, 0.044 mmol, 0.1 equiv) and K_3PO_4 (9.4 mg, 0.044 mmol, 0.1 equiv) in 0.5 ml dry DMF were stirred for 10 min at room temperature to form a first mixture. Imidazole (30 mg, 0.441 mmol) in 1 ml dry DMF and ZnO (43.0 mg, 0.529 mmol, 1.2 equiv) were added consecutively to the first mixture under argon to form a second mixture. The second mixture was stirred for an additional 10 min. CuI (167.8 mg, 0.881 mmol, 2 equiv) and followed by phenyl iodide (107.9 mg, 0.529 mmol, 1.2 equiv), which was dissolved in 0.5 ml dry DMF, were added to the second mixture to form a third mixture. The third mixture was heated to 150 °C under argon. The reaction propagation was monitored by TLC and upon completion (after about 12 hours, when

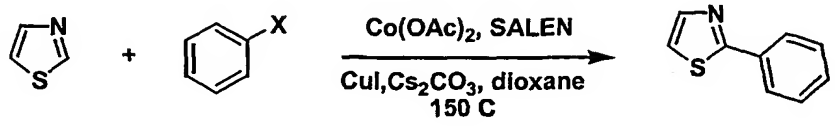
the relative amount of desired product reached its maxiumum, longer reaction times may lead to further arylation of the product) of the reaction, the resulting reaction mixture was diluted with $CHCl_3$ (20 ml) and filtered through a pad of celite. The solvents were evaporated and the product (49.6 mg, 78 %) was isolated by flash column chromatography (gradient elution hexanes → 20 % ethyl acetate / 80 % hexanes).

Example 5: Catalytic arylation of thiazole at C-5 with $Co(OAc)_2$ / IMes



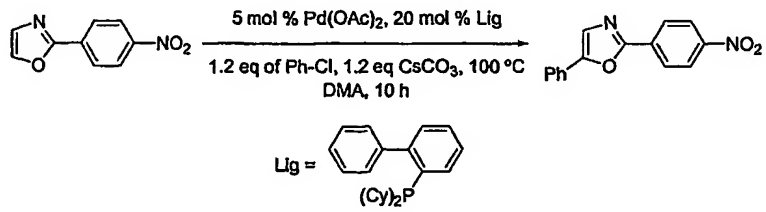
In a flame dried flask, anhydrous $Co(OAc)_2$ (3.7 mg, 0.021 mmol, 5 mol %), 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (14.0 mg, 0.041 mmol, 0.1 equiv) and K_3PO_4 (8.8 mg, 0.041 mmol, 0.1 equiv) in 0.5 ml dry DMF were stirred for 10 min at room temperature to form a first mixture. Thiazole (35 mg, 0.411 mmol) in 1 ml dry DMF and anhydrous Cs_2CO_3 (160.7 mg, 0.493 mmol, 1.2 equiv) were added consecutively to the first mixture under argon to form second mixture. Phenyl iodide (100.7 mg, 0.493 mmol, 1.2 equiv), which was dissolved in 0.5 ml dry DMF, was added dropwise to the second mixture to form third mixture. The third mixture was heated to 150 °C under argon. The reaction propagation was monitored by TLC and upon completion (after about 12 hours, when the relative amount of desired product reached its maximum, longer reaction times may lead to further arylation of the product) of the reaction, the resulting reaction mixture was diluted with $CHCl_3$ (20 ml) and filtered through a pad of celite. The solvents were evaporated and the product (42.4 mg, 64 %) was isolated by flash column chromatography (gradient elution hexanes → 10 % ethyl acetate / 90 % hexanes).

Example 6: Catalytic arylation of thiazole at C-2 with $Co(OAc)_2$ / SALEN / CuI



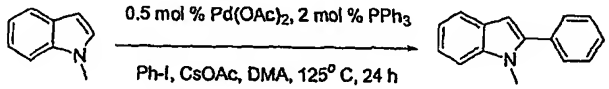
In a flame dried flask, anhydrous $Co(OAc)_2$ (3.7 mg, 0.021 mmol, 5 mol %) and SALEN [ethylenebis(salicylimine)] (11.0 mg, 0.041 mmol, 0.1 equiv) in 0.5 ml dry dioxane were stirred for 10 min at room temperature to form first mixture. Thiazole (35 mg, 0.411 mmol) in 1 ml dry dioxane, anhydrous Cs_2CO_3 (160.7 mg, 0.493 mmol, 1.2 equiv) and CuI (156.5 mg, 0.822 mmol, 2 equiv) were added consecutively to the first mixture under argon to form second mixture. Phenyl iodide (100.7 mg, 0.493 mmol, 1.2 equiv), which was dissolved in 0.5 ml dry dioxane, was added dropwise to the second mixture to form a third mixture. The third mixture was heated to 150 °C under argon. The reaction propagation was monitored by TLC and upon completion (after about 10 hours, when the relative amount of desired product reached its maxiumum, longer reaction times may lead to further arylation of the product) of the reaction, the resulting reaction mixture was diluted with $CHCl_3$ (20 ml) and filtered through a pad of celite. The solvents were evaporated and the product (57.7 mg, 87 %) was isolated by flash column chromatography (gradient elution hexanes → 10 % ethyl acetate / 90 % hexanes).

Example 7: Catalytic arylation of oxazoles with $Pd(OAc)_2$



In a 8 mL vial fitted with a setpa closure, cesium carbonate (103 mg, 0.32 mmol) was dried for at least 2 hours under vacuum at 150° C. Once dried, the base was cooled to ambient temperature, then palladium acetate (3 mg, 1.3 x 10^{-2} mmol) and 2-(dicyclohexylphosphino)biphenyl (18.4 mg, 5.3 x 10^{-2} mmol) were added under argon followed by 800 microliters (μL) of dimethylacetamide to form the first mixture. In a separate flame dried vial, 2-(4'-nitrophenyl)oxazole (50 mg, 0.263 mmol) and 800 μL of dimethylacetamide were mixed under argon to form the second mixture. The second mixture was then added to the first mixture to form the third mixture, and then chlorobenzene (35.6 mg, 0.32 mmol) was added to the third mixture to form the fourth mixture. The fourth mixture was heated to 100° C with stirring until complete (about 10 hours). 4-Phenyl-2-(4'-nitrophenyl)oxazole was isolated by flash chromatography (40 % ethyl acetate / 60 % hexanes) in 77 % yield (0.20 mmol).

Example 8: Catalytic arylation of *N*-functionalized indoles with $Pd(OAc)_2$



In a 8 mL vial fitted with a septa closure, cesium acetate (350 mg, 1.8 mmol) was dried for at least 2 hours under vacuum at 125° C. Once dried, the base was cooled to ambient temperature, then palladium acetate (1 mg, 4.6 x 10^{-3} mmol) and triphenylphosphine (4.8 mg, 1.8 x 10^{-2} mmol) were added under argon to form the first mixture. To the first mixture was added 120 μL of dimethylacetamide, followed by *N*-methylindole (119.5 mg, (0.91 mmol) and iodobenzene (223.3 mg, 1.1 mmol) to form second mixture. The second mixture was then heated to 125° C with stirring for 24 hrs. Upon completion, the reaction was diluted with dichloromethane (15 mL) filtered through celite, and the solvent was evaporated. The final product was isolated by flash column chromatography (5% ethylacetate, 95 % hexane) to give 88 % yield

(0.8 mmol) of 2-phenyl-1-methylindole.

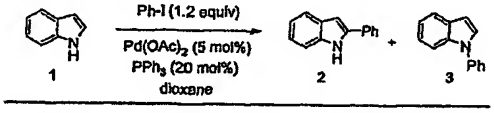
Tables 1-11 show data regarding certain embodiments of the present invention. Tables 1-2 illustrate embodiments of the present invention performed on different heteroaromatic compounds, with resulting yields and products. Table 1 displays example embodiments, regioselectivity and resulting yields for palladium-catalyzed arylation of NH-Hetero-Arenes. Table 2 displays example embodiments, regioselectivity and resulting yields for cobalt-catalyzed NH-Hetero-Arenes. Such cobalt catalyzed reactions are desireable because of the comparative low cost of the cobalt catalysts.

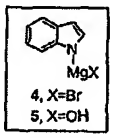
Tables 3-6 illustrate data relating to the optimization of embodiments of the present invention. Studies were carried out *N*-functionalized Indoles. Variables including ligands, the leaving group of the Ar-X compound, the basic compound and the loading of the catalyst were varied under controlled conditions. Table 3 displays the effects of variating the Ar-X compound. In certain embodiments of the present invention, chlorobenzene was determined to be a better performing Ar-X compound. Table 4 displays the results of varying ligands with the arylation of *N*-methylindole. Table 5 displays two charts showing the results of varying the basic compound in two different arylations of *N*-methylindole. In these embodiments, cesium acetate proved to be a better performing basic compound. Table 6 displays two charts reflecting the optimization of catalyst loadings. Chart a shows the yield increased until 0.1 mol % and chart b shows a increase in turnover numbers ranging from 88 to 3700 TON.

Tables 7-11 display additional embodiments of the present invention. Table 7 shows specific reactions of indoles with additional functional groups on the aryl species and the indole. Table 8 shows functional group tolerance of the arylation of oxazole. Table 9 shows the arylation of oxazole utilizing other aryl-donors. Table 10 and 11 show, the selective arylation of 2-phenylimidazole in the 4 and 2 position.

Table 1: Palladium-Catalyzed Arylation of NH-Hetero-Arenes

Chart A: Metalation as N-Protection and Activation of Heteroarenes[a]





BASE (1.2 equiv)	Isolated yield (2 / 3)
LiOH or NaOMe	0 / 0 %
K_3PO_4 or KOAc	0 / 0 %
Cs_2CO_3	0 / 5%
MgO	53 / 0%
EtMgBr[a]	65 / 0%
ZnO	44 / 0%

[a] Conditions: 150 °C, 15 h. (a) Indolyl Grignard salt 4 was prepare prior to the arylation reaction.

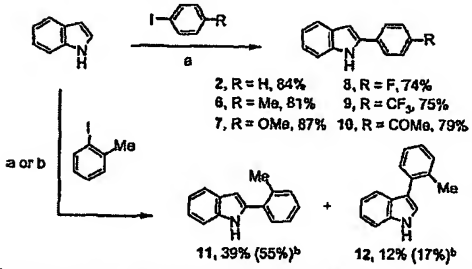


Chart B: Scope of free indole arylation. Conditions: (a) Ar–I (1.2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (20 mol %), MgO (1.2 equiv), dioxane/DMF (1:2). 150 °C, 18 h. (b) 2.5 equiv of 2-MeC_6H_4–I.

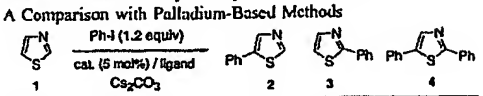
Chart C: Highly Selective C-Arylation of Free (NH)-Azoles[a]

entry	substrate	condition	product	yield
1		Ph-I (1.2 equiv), a		88%
2		a		81%
3		a		81%
4		a		72%
5		a + CuI (2 equiv)		83%
6		a + CuI (0.2 equiv)		90%
7		a + CuI (0.2 equiv)		78%

[a] Conditions: (a) PhI (1.2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (20 mol %), MgO (1.2 equiv), dioxane, 150 °C, 12–15 h. PhBr afforded 52–60% yield of the corresponding products.

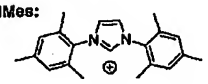
Table 2: Cobalt-Catalyzed Arylation of NH-Hetero-Arenes

Chart A: Cobalt-Catalyzed Arylation of Thiazole: A Comparison with Palladium-Based Methods

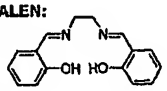


entry	conditions	yield
1	$Co(OAc)_2$, IMes (10 mol%), DMF, 150 °C, 12 h	64 / 0 / 0 % (42% with Ph-Br)
2	$Co(OAc)_2$, (+/-) Ph_3P (20 mol%), DMF, 150 °C, 12 h	traces
3	$Co(OAc)_2$, IMes (10 mol%), dioxane, 120 °C, 10 h + CuI (2 equiv)	0 / 84 / 0 %
4	$Co(OAc)_2$, SALEN (10 mol%), dioxane, 120 °C, 10 h + CuI (2 equiv)	0 / 87 / 0 % (76% with Ph-Br)

IMes:

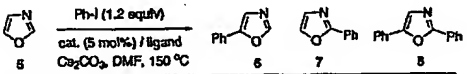


SALEN:



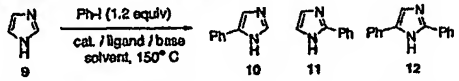
$Cl^{\ominus}$ / K_3PO_4

Chart B: Cobalt-catalyzed Arylation of Oxazole:



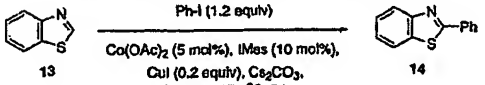
entry	conditions	yield
1	$Co(OAc)_2$, IMes (10 mol%) DMF, 12 h	34 / 6 / 0 %
2	$Co(OAc)_2$, IMes (10 mol%), 100 °C, 10 h, + CuI (2 equiv)	0 / 73 / 0 % (58% with Ph-Br)
3	$Co(OAc)_2$, SALEN (10 mol%) dioxane, 10 h, + CuI (2 equiv)	0 / 53 / 8 %

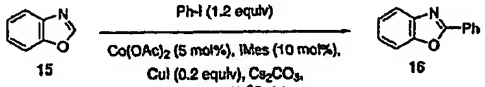
Chart C: C-Arylation of Imidazole: A Comparison of Cobalt- and Palladium-Based Methods



entry	conditions	yield
1	$Co(OAc)_2$ (5 mol%) IMes (10 mol%) ZnO (1.2 equiv), DMF, 12 h	41 / 0 / 0 %
2	$Co(OAc)_2$ (5 mol%) IMes (10 mol%) ZnO (1.2 equiv), DMF, 12 h + CuI (2 equiv)	0 / 78 / 0 %

Chart D: Cobalt-Catalyzed Arylation of Benzazoles





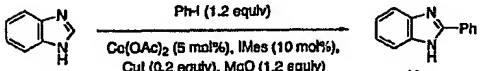


Table 3: Effect of Ar-X compound on Arylation of *N*-methylindole

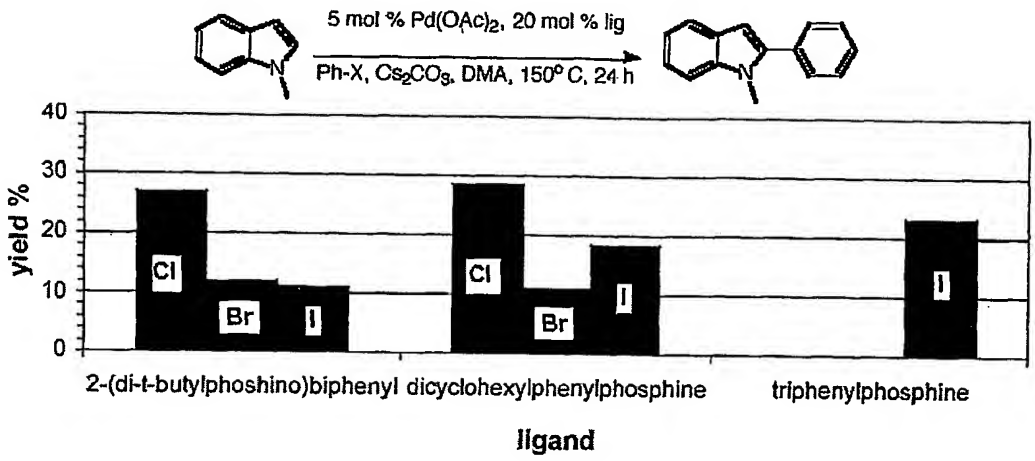


Table 4: Ligand Screen in Arylation of *N*-methylindole

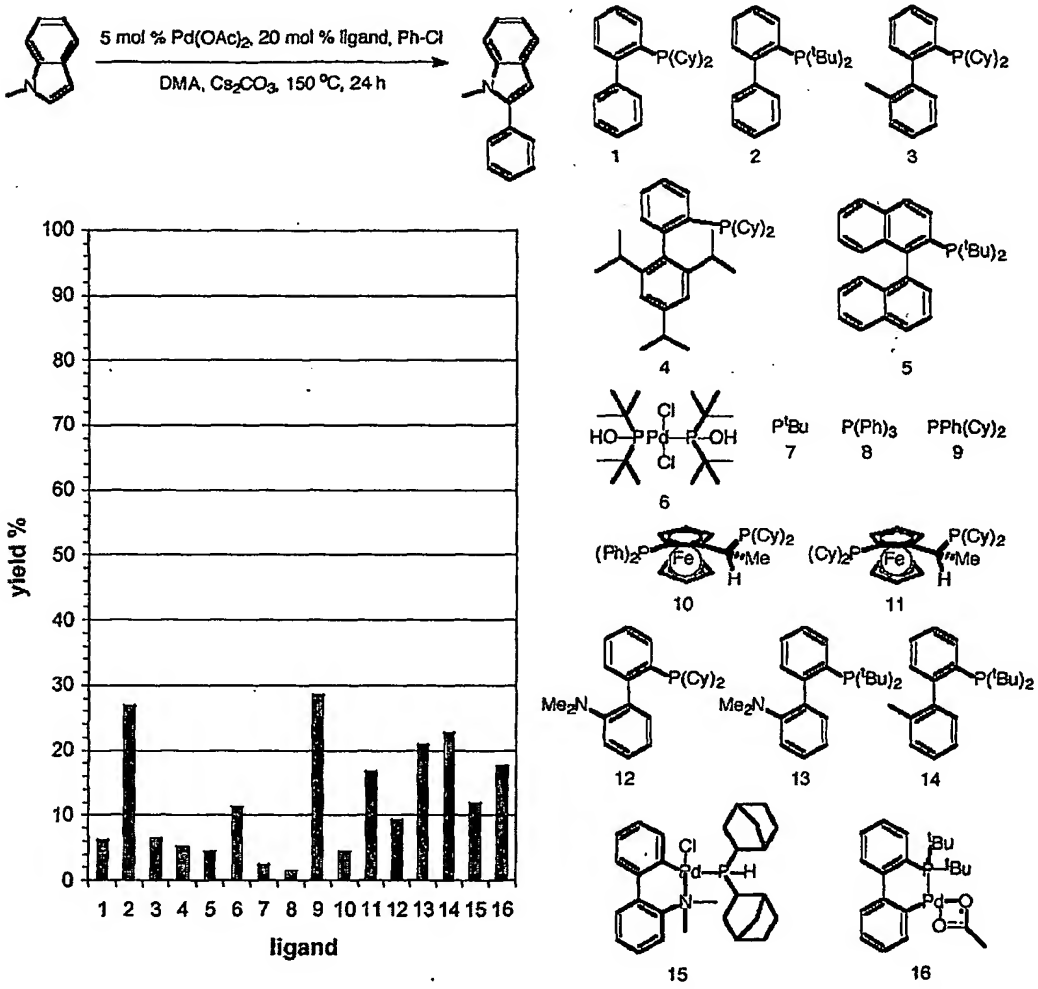
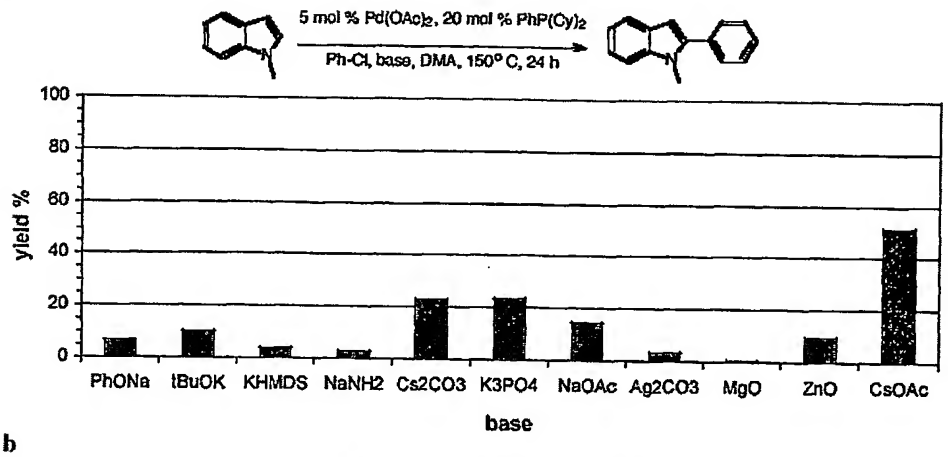
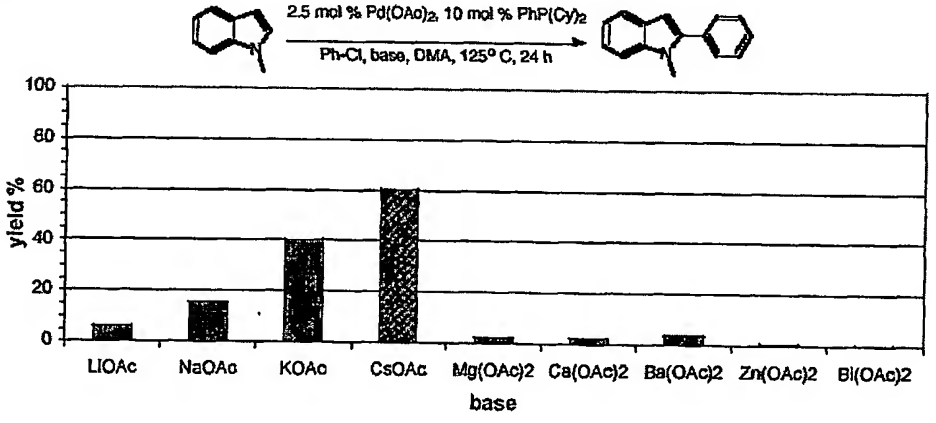


Table 5: Effect of Basic Compound on Arylation of *N*-Methylindole

a



b



5

Table 6: Optimization of Catalyst Loading in Arylation of *N*-methylindole

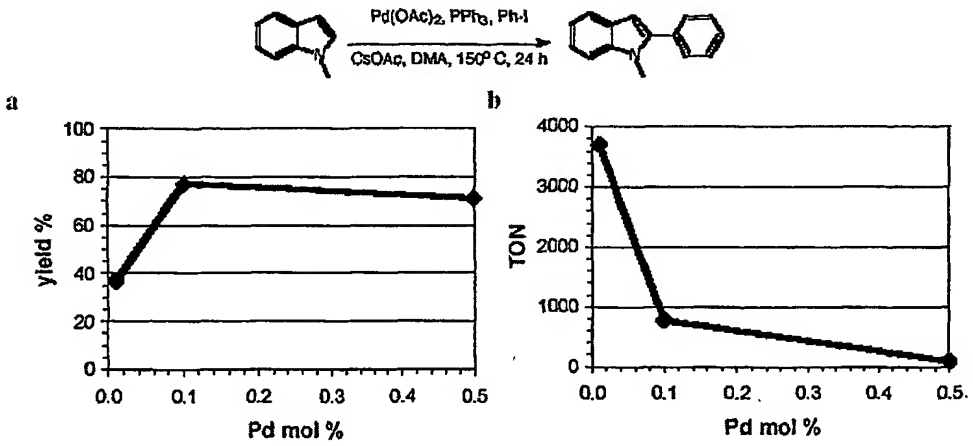
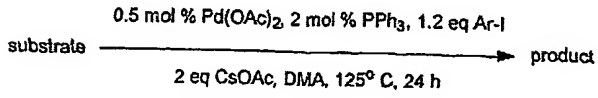
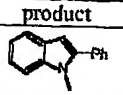
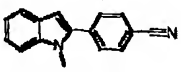
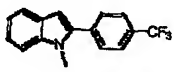
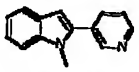
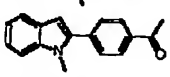
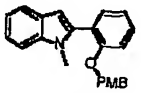
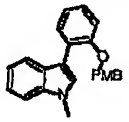
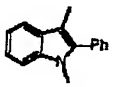
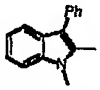
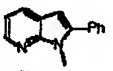
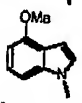
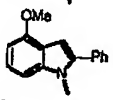
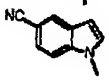
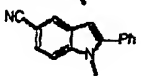
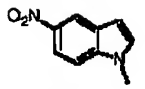
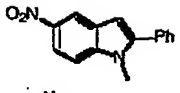
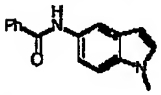
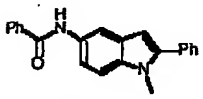
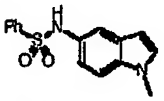
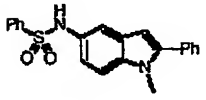
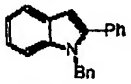
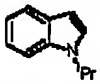
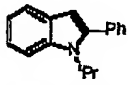
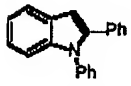
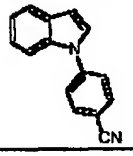
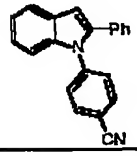


Table 7: Results for Direct Arylation of Indole substrates

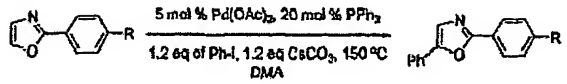


entry	substrate	product	Yield %[a]
1			88 (54)[b]
2			71
3			62
4			73
5			52
6			15 (29)[c]
			26 (38)[c]
7			31
8			21
9			85
10			51
11			78

12			61
13			38
14			24 (50)[d]
15			81
16			92
17			68
18			55

[a] All values based on isolated yields. [b] Chlorobenzene used as donor. [c] 150 °C used. [d] 0.1 mol % $Pd(OAc)_2$ used and reaction run for 48 hours.

Table 8: Functional Group Tolerance of the Arylation of Oxazole



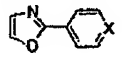
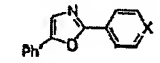
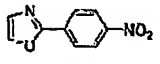
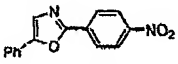
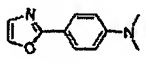
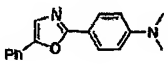
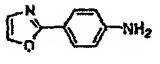
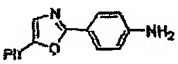
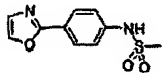
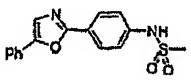
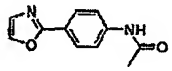
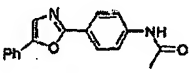
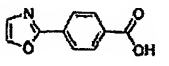
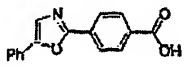
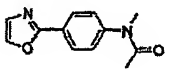
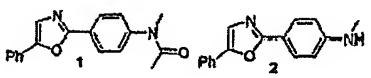
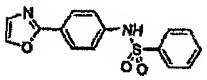
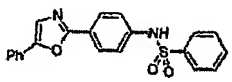
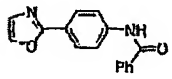
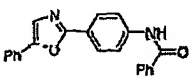
substrate	product(s)	yield % / notes
		X = H; 87 % DMF used, 120 °C X = N; 66 % DMF used
		76 % 160 °C
		63%
		66% 100 °C
		25 %
		17 %
		No RXN
		12% 1; 73% 2
		61 %
		87% 105 °C

Table 9: Arylation of Oxazole Utilizing Other Aryl-Donors

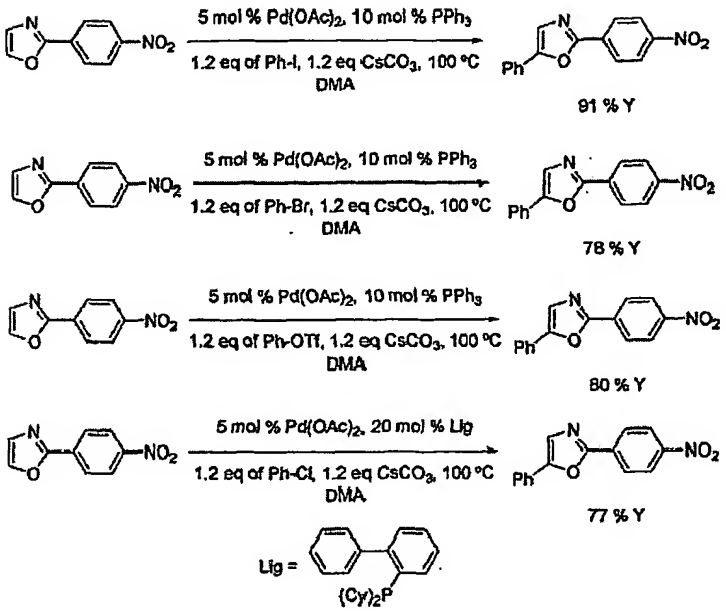
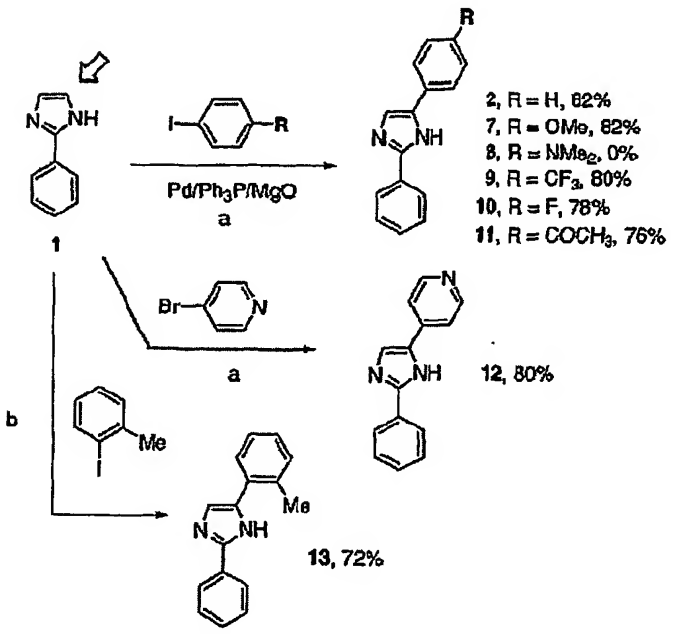
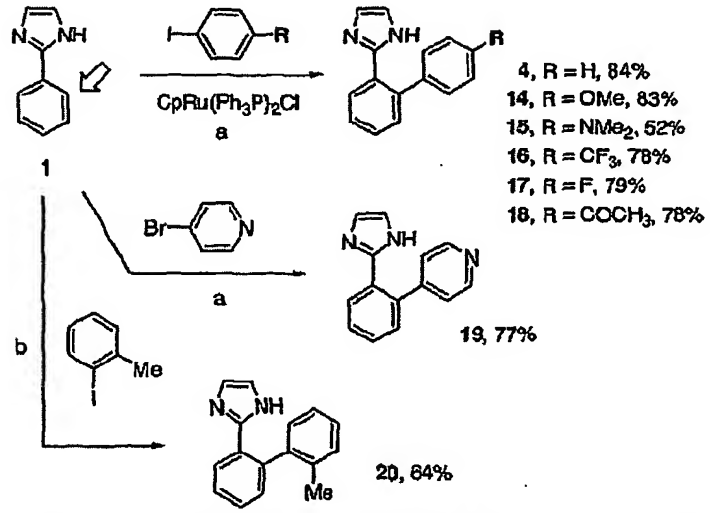


Table 10: Selective 4-Arylation of 2-Phenylimidazole



[a] Conditions: (a) Ar-X (1.2 equiv), $Pd(OAc)_2$ (5 mol %), Ph_3P (20 mol %), MgO (1.2 equiv), dioxane, 150 °C. (b) The same as conditions a except that 1.8 equiv of 2-Me-C_6H_4-I was used.

Table 11: Selective 2'-Arylation of 2-Phenylimidazole



[a] *Conditions*: (a) Ar-X (1.8 equiv), $CpRu(Ph_3P)_2Cl$ (5 mol %), Cs_2CO_3 (1.2 equiv), DMF, 130 °C. (b) The same as conditions a except that 2.4 equiv of 2-Me-C_6H_4-I was used.

Thus, the present invention is well adapted to carry out the objects and attain the ends and advantages mentioned as well as those which are inherent therein. While numerous changes may be made by those skilled in the art, such changes are encompassed within the spirit and scope of this invention as defined by the appended claims.

WHAT IS CLAIMED IS:

1. A method for the direct arylation of carbon-hydrogen sites on a heteroaromatic compound comprising:

contacting the heteroaromatic compound with a basic compound to form a first mixture;

adding a second mixture comprising a catalyst to the first mixture to form a third mixture; and

adding an Ar-X compound to the third mixture, wherein Ar comprises an aryl species and X comprises a leaving group.

2. The method of Claim 1 wherein the second mixture further comprises a carbon selectivity agent.

3. The method of Claim 2 wherein the carbon selectivity agent comprises copper iodide.

4. The method of Claim 1 further comprising heating the third mixture.

5. The method of Claim 1 further comprising purifying the third mixture.

6. The method of Claim 1 wherein the heteroaromatic compound comprises an aromatic ring having at least one non-carbon element as part of the ring, wherein the non-carbon element is selected from the group consisting of oxygen, sulfur, nitrogen and phosphorous.

7. The method of Claim 6 wherein the heteroaromatic compound further comprises one or more functional groups located outside of the ring.

8. The method of Claim 1 wherein the heteroaromatic compound is selected from the group consisting of indoles, imidazoles, pyrroles, oxazoles,

pyrazoles, triazoles, tetrazoles, thioazoles, benzimidazole, benzthiazoles and combinations thereof.

9. The method of Claim 1 wherein the basic compound is selected from the group consisting of oxides, carbonates, carboxylates and salts.

10. The method of Claim 1 wherein the basic compound is selected from the group consisting of magnesium oxide, zinc oxide, cesium carbonate, cesium acetate and potassium acetate.

11. The method of Claim 11 wherein the catalyst comprises a transition metal catalyst.

12. The method of Claim 11 wherein the transition metal catalyst is selected from the group consisting of palladium, cobalt and mixtures thereof.

13. The method of Claim 11 wherein the transition metal catalyst is selected from the group consisting of palladium acetate, cobalt acetate and mixtures thereof.

14. The method of Claim 11 wherein the transition metal catalyst is selected from the group consisting of ruthenium, rhodium, iridium and mixtures thereof.

15. The method of Claim 1 wherein the mixture further comprises at least one transition metal ligand.

16. The method of Claim 15 wherein the transition metal ligand is selected from the group consisting of phosphine ligands, SALEN, nitrogen ligands and carbene ligands.

17. The method of Claim 1 wherein the leaving group is selected from the group of halogens consisting of iodine, bromine, chlorine and fluorine.

18. The method of Claim 1 wherein the leaving group comprises triflate.

19. The method of Claim 1 further comprising adding a dipolar aprotic solvent to the first mixture.

20. A palladium-catalyzed method for selectively arylating a N-H heteroaromatic compound having at least a first carbon-hydrogen site and a second carbon-hydrogen site for arylation, said method comprising:

forming a mixture comprising the heteroaromatic compound and a basic compound;

adding a palladium catalyst to the mixture;

adding a carbon selectivity agent to the mixture if arylation is desired on the second carbon-hydrogen site; and

adding an Ar-X compound to the mixture.

21. The method of Claim 20 wherein the N-H heteroaromatic compound is selected from the group consisting of indoles, imidazoles, 2-arylimidazole, 4-phenylimidazol, benzimidazole, pyrroles, and pyrazoles.

22. The method of Claim 20 wherein the palladium catalyst comprises palladium acetate.

23. The method of Claim 20 wherein the carbon selectivity agent is copper iodide.

24. The method of Claim 20 wherein the basic compound comprises magnesium oxide or zinc oxide.

25. The method of Claim 20 further comprising adding a phosphine ligand to the mixture.

26. A cobalt-catalyzed method for the selective arylation of an imidazole having at least a first carbon-hydrogen site and a second carbon-hydrogen site for arylation, said method comprising:

forming a mixture comprising the imidazole compound and a basic compound;

adding a cobalt catalyst to the mixture;

adding a carbon selectivity agent to the mixture if arylation is desired on the second carbon-hydrogen site; and

adding an Ar-X compound to the mixture.

27. The method of Claim 26 wherein the imidazole comprises a derivative of imidazole.

28. The method of Claim 26 wherein the cobalt catalyst comprises cobalt acetate.

29. The method of Claim 26 wherein the carbon selectivity agent is copper iodide.

30. The method of Claim 26 wherein the basic compound comprises magnesium oxide or zinc oxide.

31. The method of Claim 26 further comprising adding a ligand to the mixture, wherein the ligand is selected from the group consisting of SALEN and IMes.

32. A cobalt-catalyzed method for the selective arylation of a heteroaromatic compound that does not have a free N-H site, the heteroaromatic compound having at least a first carbon-hydrogen site and a second carbon-hydrogen

site for arylation, said method comprising:

forming a mixture comprising the heteroaromatic compound and a basic compound;

adding a cobalt catalyst to the mixture;

adding a carbon selectivity agent to the mixture if arylation is desired on the second carbon-hydrogen site; and

adding an Ar-X compound to the mixture.

33. The method of Claim 32 wherein the heteroaromatic compound that does not have a free N-H site is selected from the group consisting of oxazoles, thiazoles, benzoxazoles and benzthiazoles.

34. The method of Claim 32 wherein the cobalt catalyst comprises cobalt acetate.

35. The method of Claim 32 wherein the basic compound comprises cesium carbonate.

36. The method of Claim 32 further comprising adding a ligand to the mixture, wherein the ligand is selected from the group consisting of SALEN and IMes.

37. A method for the selective arylation of an oxazole having at least a first carbon-hydrogen site and a second carbon-hydrogen site for arylation, said method comprising:

forming a mixture comprising the oxazole and a basic compound;

adding a catalyst to the mixture;

adding a carbon selectivity agent to the mixture if arylation is desired on the second carbon-hydrogen site; and

adding an Ar-X compound to the mixture.

38 The method of Claim 37 wherein the oxazole comprises a 2-functionalized oxazole.

39. The method of Claim 37 wherein the catalyst comprises palladium acetate.

40. The method of Claim 37 wherein the basic compound comprises cesium carbonate.

41. The method of Claim 37 further comprising adding a ligand to the mixture, wherein the ligand comprises 2-(dicyclohexylphosphino)biphenyl.

42. The method of Claim 37, wherein the Ar-X compound comprises an arylchloride.

43. A method for the selective arylation of a N-functionalized indole having at least a first carbon-hydrogen site and a second carbon-hydrogen site for arylation, said method comprising:

forming a mixture comprising the N-functionalized indole and a basic compound;

adding a catalyst to the mixture;

adding a carbon selectivity agent to the mixture if arylation is desired on the second carbon-hydrogen site; and

adding an Ar-X compound to the mixture.

44. The method of Claim 43 wherein the catalyst comprises palladium acetate.

45. The method of Claim 43 wherein the basic compound comprises cesium acetate.

46. The method of Claim 43 wherein the Ar-X comprises and aryl species and a leaving group, wherein the leaving group is selected from the group of halogens consisting of iodine, bromine, chlorine and fluorine.

47. The method of Claim 43 wherein the AR-X compound comprises an aryl chloride.

48. The method of Claim 47 further comprising adding a ligand to the mixture, wherein the ligand comprises dicyclohexylphenyl phosphine.

49. A method of making a pharmaceutical product comprising:

contacting a heteroaromatic compound with a basic compound to form a first mixture;

adding a second mixture comprising a catalyst to the first mixture to form a third mixture; and

adding an Ar-X compound to the third mixture, wherein Ar comprises an aryl species and X comprises a leaving group.

50. A method of making a dye comprising:

contacting a heteroaromatic compound with a basic compound to form a first mixture;

adding a second mixture comprising a catalyst to the first mixture to form a third mixture; and

adding an Ar-X compound to the third mixture, wherein Ar comprises an aryl species and X comprises a leaving group.

51. The method of Claim 50 wherein the dye comprises a fluorescent dye.

52. The method of Claim 50 wherein the dye comprises a brightner.

53. The method of Claim 50 wherein the dye comprises a dye used for

liquid crystal materials.

54. The method of Claim 50 wherein the dye comprises a dye used for paint products.

55. A method of making a nanotechnology material comprising:

contacting a heteroaromatic compound with a basic compound to form a first mixture;

adding a second mixture comprising a catalyst to the first mixture to form a third mixture; and

adding an Ar-X compound to the third mixture, wherein Ar comprises an aryl species and X comprises a leaving group.

56. The method of Claim 55 wherein the nanotechnology material comprises a material used in a single molecule information storage device.

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